PERGAMON

Food and Chemical Toxicology 40 (2002) 113–131

www.elsevier.com/locate/foodchemtox

Research Section

Evaluation of the potential effects of ingredients added to cigarettes. Part 4: subchronic inhalation toxicity☆

P.M. Vanscheeuwijck[a,*], A. Teredesai[b], P.M. Terpstra[a], J. Verbeeck[a], P. Kuhl[b], B. Gerstenberg[b], S. Gebel[b], E.L. Carmines[c]

[a]*CRC Contract Research Center[1], Tollaan 101c, B-1932 Zaventem, Belgium*
[b]*INBIFO Institut für Biologische Forschung[1], Fuggerstr. 3, D-51149 Köln, Germany*
[c]*Philip Morris U.S.A., Research Center, Richmond, VA 23261-6583, USA*

Accepted 1 July 2001

Abstract

Mainstream smoke from blended research cigarettes with (test) and without (control) the addition of ingredients to the tobacco was assayed for inhalation toxicity. In total, 333 ingredients commonly used in cigarette manufacturing were assigned to three different groups. Each group of ingredients was introduced at a low and a high level to the test cigarettes. Male and female Sprague–Dawley rats were exposed nose-only either to fresh air (sham) or diluted mainstream smoke from the test, the control, or the Reference Cigarette 1R4F at a concentration of 150 μg total particulate matter/l for 90 days, 6 h/day, 7 days/week. A 42-day post-inhalation period was included to evaluate reversibility of possible findings. There were no remarkable differences in in-life observations or gross pathology between test and control groups. An increase in activity of liver enzymes, known to be due to the high smoke dose, revealed no toxicologically relevant differences between the test and control groups. No toxicological differences were seen between the test and control groups for smoke-related hematological changes, such as a decrease in total leukocyte count. The basic smoke-related histopathological effects, which were more pronounced in the upper respiratory tract than in the lower respiratory tract, were hyperplasia and squamous metaplasia of the respiratory epithelium, squamous metaplasia and atrophy of the olfactory epithelium, and accumulation of pigmented alveolar macrophages. There were no relevant qualitative or quantitative differences in findings in the respiratory tract of the rats exposed to the smoke from the control and test cigarettes. The data indicate that the addition of these 333 commonly used ingredients, added to cigarettes in three groups, did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Tobacco; Ingredient; Flavor; Cigarette smoke; Biological activity; Subchronic inhalation

1. Introduction

Ingredients are used in cigarette manufacturing to smooth or intensify taste, odor or pungency of the smoke (Triest, 1979). Cigarette manufacturers have used ingredients for many years, and a complete list of important ingredients used by the major US tobacco companies was published in 1994 (TR Staff Report, 1994). Individual ingredients are added to tobacco filler at relatively low levels, usually 2% or less; hence, their contribution to the composition of cigarette smoke is expected to be low. Some of these ingredients are volatile and may be transferred unchanged into cigarette smoke. Other less volatile ones may be subject to pyrolysis and combustion (Hoffman and Hoffman, 1997), and this has raised concern about potential biological activity in ingredient-supplemented cigarette products.

The effects of some of these ingredients as single ingredients or mixtures of ingredients in cigarette mainstream smoke (MS) have been evaluated (Gaworski et al., 1997); however, the effects of many of the ingredients were not thoroughly evaluated in an inhalation study, and the effects that might result from the addition of

Abbreviations: 5′HCOT, 5′-hydroxycotinine; c3′HCOT, *cis*-3′-hydroxycotinine; CMH, Cochran–Mantel–Haenszel test; CO, carbon monoxide; COT, cotinine; GSD, geometrical standard deviation; HbCO, carboxyhemoglobin; HE, hematoxylin–eosin; IARC, International Agency for Research on Cancer; IG, ingredient group; ISO, International Organization for Standardization; MMAD, mass median aerodynamic diameter; MS, mainstream smoke; NCOT, norcotinine; NNIC, nornicotine; NN′O, nicotine-*N*′-oxide; OECD, Organisation for Economic Cooperation and Development; ppm, parts per million; RSD, relative standard deviation; S.D., standard deviation; t3′HCOT, *trans*-3′-hydroxycotinine; TPM, total particulate matter

☆ Portions of the results of this work were presented at the 39th Annual Meeting of the Society of Toxicology in Philadelphia, PA, USA.

* Corresponding author. Tel.: +32-2-721-5047; fax: +32-2-725-1209.
E-mail address: Vanscheeuwijck.Patrick@pmintl.ch (P.M. Vanscheeuwijck).

[1] CRC and INBIFO are Philip Morris research laboratories.

0278-6915/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0278-6915(01)00089-8

PM3001115335

Source: https://www.industrydocuments.ucsf.edu/docs/fmxk0001